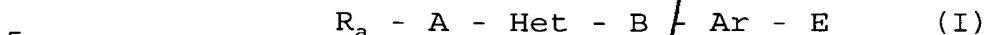


What is claimed is:

1. A compound of the formula I



wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno
10 moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, wherein a methylene group, linked either to the group Het or Ar, may be replaced by an
15 oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-6} -alkyl group,

20 E denotes a cyano or $R_b\text{NH}-C(=\text{NH})-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a C_{1-3} -alkyl group or a group which may be cleaved in vivo,

25

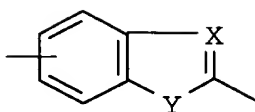
Ar denotes a phenylene or naphthylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl C_{1-3} -alkyl or C_{1-3} -alkoxy group,

30

a thienylene, thiazolylene, pyridinylen, pyrimidinylene, pyrazinylen or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3} -alkyl group,

Het denotes a bicyclic heterocycle of formula

35



, wherein

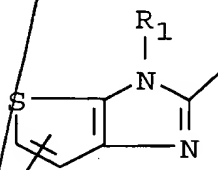
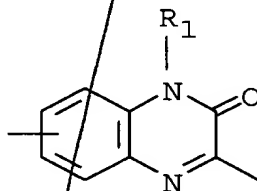
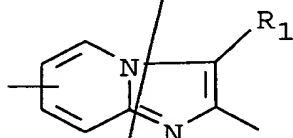
X is a nitrogen atom and

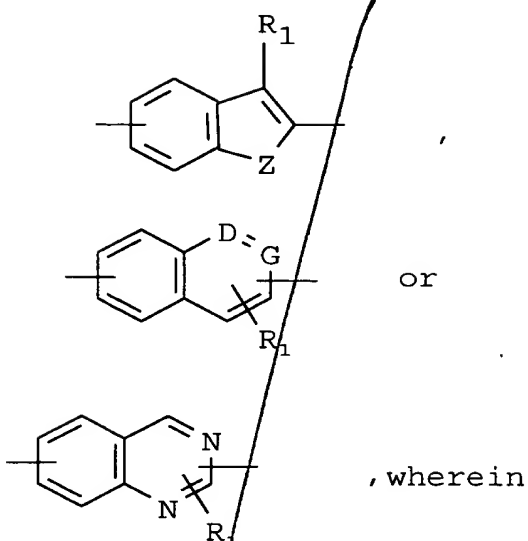
5 Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C₁₋₆-alkyl or C₃₋₇-cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the above-mentioned bicyclic heterocycle may each be
10 replaced by a nitrogen atom,

or X denotes a methyne group optionally substituted by the group R₁, wherein R₁ is as hereinbefore defined, and

15 Y denotes a nitrogen atom optionally substituted by a C₁₋₆-alkyl or C₃₋₇-cycloalkyl group,

or Het denotes a group of the formula





R_1 is as hereinbefore defined,

Z denotes an oxygen or sulphur atom,

one of the groups D or G denotes a nitrogen atom and the other group D or G denotes a methyne group,

and R_a denotes a C_{1-6} -alkyl group, a C_{3-7} -cycloalkyl group optionally substituted by a C_{1-3} -alkyl group, wherein the C_{1-3} -alkyl group may additionally be substituted by a carboxyl group or by a group which may be converted *in vivo* into a carboxy group,

or an R_2NR_3 - group wherein

R_2 denotes a C_{1-4} -alkyl group, which may be substituted by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3} -alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonyl amino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl group,

a C₂₋₄-alkyl group substituted by a hydroxy, phenyl-
C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, C₁₋₃-
alkoxycarbonyl-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-carboxy-
C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-C₁₋₃-alkoxycarbonyl-C₁₋₃-
5 alkylamino group, whilst in the abovementioned groups
the carbon atom in the α -position relative to the
adjacent nitrogen atom may not be substituted, or

a piperidinyl group optionally substituted by a
10 C₁₋₃-alkyl group and

R₃ denotes a hydrogen atom, a C₁₋₆-alkyl group, a
C₃₋₇-cycloalkyl group optionally substituted by a
C₁₋₃-alkyl group, a C₃₋₆-alkenyl or alkynyl group,
15 wherein the unsaturated part may not be linked
directly to the nitrogen atom of the R₂NR₃- group,
a phenyl group optionally substituted by a fluorine,
chlorine or bromine atom or by a C₁₋₃-alkyl or
C₁₋₃-alkoxy group, a benzyl, oxazolyl, isoxazolyl,
20 thiazolyl, isothiazolyl, pyrazolyl, pyridinyl,
pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, thienyl
or imidazolyl group or

R₂ and R₃ together with the nitrogen atom between them
25 denote a 5- to 7-membered cycloalkyleneimino group,
optionally substituted by a carboxymethyl or
C₁₋₄-alkoxycarbonyl group, onto which a phenyl ring may
additionally be fused,

30 or a tautomer or salt thereof.

2. A compound of the formula I according to claim 1,
wherein

35 A denotes a carbonyl or sulphonyl group linked to the
benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno

moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, in which a methylene group, linked either to the group Het or Ar, may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-5} -alkyl group,

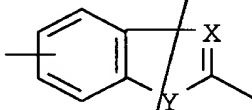
E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a C_{1-3} -alkyl group or a group which may be cleaved *in vivo*,

Ar denotes a phenylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3} -alkyl or C_{1-3} -alkoxy group,

a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3} -alkyl group,

Het denotes a bicyclic heterocycle of formula



, wherein

X is a nitrogen atom and

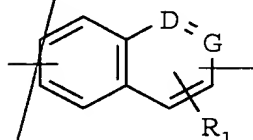
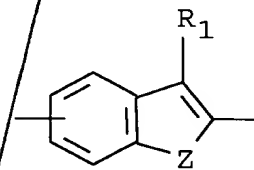
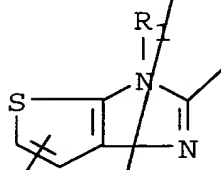
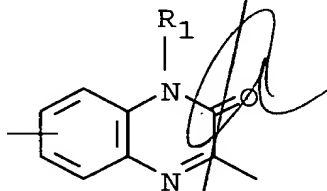
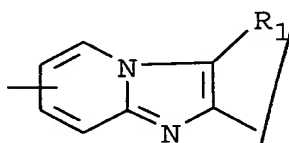
Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C_{1-6} -alkyl or C_{3-7} -cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the

above-mentioned bicyclic heterocycle may each be replaced by a nitrogen atom,

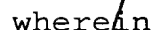
or X denotes a methyne group optionally substituted by the group R_1 , wherein R_1 is as hereinbefore defined, and

Y denotes a nitrogen atom optionally substituted by a C_{1-6} -alkyl or C_{3-7} -cycloalkyl group,

or Het denotes a group of the formulae



or



30 a C₂₋₄-alkyl group substituted by a hydroxy, phenyl-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino group, whilst in the abovementioned groups the carbon atom in the α -position relative to the adjacent nitrogen atom may not be substituted, or

a piperidinyl group optionally substituted by a C₁₋₃-alkyl group and

5 R₃ denotes a hydrogen atom, a C₁₋₆-alkyl group, a C₃₋₇-cycloalkyl group optionally substituted by a C₁₋₃-alkyl group, a C₃₋₆-alkenyl or alkynyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R₂NR₃- group,

10 a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C₁₋₃-alkyl or C₁₋₃-alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl,
15 imidazolyl or piperidinyl group or

R₂ and R₃ together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxymethyl or
20 C₁₋₄-alkoxycarbonyl group, onto which additionally a phenyl ring may be fused,

or a tautomer or salt thereof.

25 3. A compound of the formula I according to claim 1, wherein

A denotes a carbonyl or sulphonyl group linked to the
30 benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R₁ group,

B denotes an ethylene group in which the methylene group
35 linked to the group Ar may be replaced by an oxygen or sulphur atom or by an -NR₁- group, wherein

R_1 denotes a hydrogen atom or a C_{1-4} -alkyl group,

E denotes an $R_bNH-C(=NH)-$ group wherein

5 R_b denotes a hydrogen atom, a hydroxy,
 C_{1-9} -alkoxycarbonyl, cyclohexyloxycarbonyl, phenyl-
 C_{1-3} -alkoxycarbonyl, benzoyl, p- C_{1-3} -alkyl-benzoyl or
pyridinoyl group, whilst the ethoxy moiety in the
2-position of the abovementioned C_{1-9} -alkoxycarbonyl
10 group may additionally be substituted by a C_{1-3} -alkyl-
sulfonyl or 2-(C_{1-3} -alkoxy)-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by
a chlorine atom or by a methyl, ethyl or methoxy group or
15 it denotes a 2,5-thienylene group,

Het denotes a 1-(C_{1-3} -alkyl)-2,5-benzimidazolylene, 1-
cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene,
1-(C_{1-3} -alkyl)-2,5-indolylene, 1-(C_{1-3} -alkyl)-
20 2,5-imidazo[4,5-b]pyridinylene, 3-(C_{1-3} -alkyl)-
2,7-imidazo[1,2-a]pyridinylene or 1-(C_{1-3} -alkyl)-
2,5-thieno[2,3-d]imidazolylene group and

R_a denotes an R_2NR_3- group wherein

25 R_2 is a C_{1-4} -alkyl group substituted by a carboxy,
 C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl,
 C_{1-3} -alkylsulphonylamino carbonyl or 1H-tetrazol-5-yl
group,

30 a C_{2-4} -alkyl group substituted by a hydroxy, benzyloxy,
carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl-
 C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino
or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino
35 group, whilst in the abovementioned groups the carbon

5 R_3 denotes a C_3-7 -cycloalkyl group, a propargyl group,
wherein the unsaturated part may not be linked directly
to the nitrogen atom of the R_2NR_3 group, a phenyl group
optionally substituted by a fluorine or chlorine atom,
or by a methyl or methoxy group, a pyrazolyl, py-
ridazolyl or pyridinyl group optionally substituted by
10 a methyl group or

or a tautomer or salt thereof

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R₁ group,

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an $-NR_1-$ group, wherein

R₁ denotes a hydrogen atom or a methyl group,

E denotes an $R_pNH-C(=NH)-$ group, wherein

5 R_b denotes a hydrogen atom or a hydroxy,
 C_{1-9} -alkoxycarbonyl, cyclohexyloxycarbonyl,
benzyloxycarbonyl, benzoyl, p- C_{1-3} -alkylbenzoyl or
nicotinoyl group, whilst the ethoxy moiety in the 2-
position of the abovementioned C_{1-9} -alkoxycarbonyl
group may additionally be substituted by a C_{1-3} -
alkylsulphonyl or 2-(C_{1-3} -alkoxy)-ethyl group,

10 Ar denotes a 1,4-phenylene group optionally substituted by
a chlorine atom or by a methyl, ethyl or methoxy group, or
it denotes a 2,5-thienylene group,

15 Het denotes a 1-methyl-2,5-benzimidazolylenes, 1-
cyclopropyl-2,5-benzimidazolylenes, 2,5-benzothiazolylenes,
1-methyl-2,5-indolylenes, 1-methyl-
2,5-imidazo[4,5-b]pyridinylenes, 3-methyl-
2,7-imidazo[1,2-a]pyridinylenes or 1-methyl-
2,5-thieno[2,3-d]imidazolylenes group and

20 R_a denotes a R_2NR_3 - group wherein

R_2 denotes a C_{1-3} -alkyl group which may be substituted
by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl,
methylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,

25 a C_{2-3} -alkyl group substituted by a hydroxy, benzyloxy,
carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl-
 C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino
or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino
30 group, whilst in the abovementioned groups the carbon
atom in the α -position to the adjacent nitrogen atom
may not be substituted, and

35 R_3 denotes a propargyl group, wherein the unsaturated
moiety may not be linked directly to the nitrogen atom
of the R_2NR_3 group, a phenyl group optionally

substituted by a fluorine or chlorine atom, or by a methyl or methoxy group or it denotes a pyridinyl group,

5 or a tautomer or salt thereof.

5. A compound of the formula I according to claim 1, wherein

10

A denotes a carbonyl group linked to the benzo or thieno moiety of the group Het,

15

B denotes an ethylene group wherein the methylene group attached to the group Ar may be replaced by an $-NR_1$ group, whilst

R_1 denotes a hydrogen atom or a methyl group,

20

E denotes an $R_bNH-C(=NH)-$ group wherein

25

R_b is a hydrogen atom, a hydroxy, C_{1-9} -alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p- C_{1-3} -alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9} -alkoxycarbonyl group may additionally be substituted by a methylsulfonyl or 2-ethoxy-ethyl group,

30

Ar denotes a 1,4-phenylene group optionally substituted by a methoxy group or it denotes a 2,5-thienylene group,

35

Het denotes a 1-methyl-2,5-benzimidazolylenes, 2,5-benzothiazolylenes, 1-methyl-2,5-indolylenes or 1-methyl-2,5-thieno[2,3-d]imidazolylenes group and

R_a denotes an R₂NR₃- group wherein

5 R₂ denotes a C₁₋₃-alkyl group which may be substituted by a carboxy, C₁₋₆-alkyloxycarbonyl, benzyloxycarbonyl, methylsulfonylaminocarbonyl or 1H-tetrazol-5-yl group,

10 a C₂₋₃-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C₁₋₃-alkylamino, C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position to the adjacent nitrogen atom may not be substituted, and

15 R₃ denotes a phenyl group optionally substituted by a fluorine atom, or it denotes a 2-pyridinyl group, or a tautomer or salt thereof.

20 6. A compound selected from the group consisting of:

25 (a) 2-[N-(4-amidinophenyl)-aminomethyl]-benzthiazole-5-carboxylic acid-N-phenyl-N-(2-carboxyethyl)-amide,

(b) 2-[N-(4-midinophenyl)-N-methyl-aminomethyl]-benzthiazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

30 (c) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

35 (d) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxycarbonylpropyl)-amide,

(e) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-
N-(hydroxycarbonylmethyl)-amide,

5

(f) 1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
hydroxycarbonylethyl)-amide,

10 (g) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
hydroxycarbonylethyl)-amide,

15 (h) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-
yl-carboxylic acid-N-(2-pyridyl)-N-(2-
hydroxycarbonylethyl)-amide,

20 (i) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-
yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-
amide,

(j) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-
yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-
amide,

25

(k) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-
tetrazol-5-yl)ethyl]-amide,

30 (l) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
hydroxycarbonylethyl)-amide,

35 (m) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-
hydroxycarbonylethyl)-amide,

(n) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

5 (o) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-hydroxycarbonylethyl-N-methyl)-2-aminoethyl]-amide,

(p) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
10 benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,

(q) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-
15 hydroxycarbonylethyl)-amide,

(r) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
20

(s) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

25 (t) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide
and

(u) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-
30 thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

or a prodrug, double prodrug or salt thereof.

35

7. 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide, or a prodrug, double prodrug or salt thereof.

5

8. 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide or a prodrug, double prodrug or salt thereof.

10

9. 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide, or a prodrug, double prodrug or salt thereof.

15

10. 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl) amide.

20

11. A physiologically acceptable salt of a compound according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 wherein E denotes an $R_pNH-C(=NH)-$ group.

25

12. A pharmaceutical composition containing a compound according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes an $R_pNH-C(=NH)-$ group, or a physiologically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

30

35

13. A method for preventing or treating venous and
arterial thrombotic disease which comprises administering
an antithrombotic amount of a compound according claim 1,
2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes an
5 $R_bNH-C(=NH)-$ group, or a physiologically acceptable salt
thereof.

14. The method of claim 13 wherein said thrombotic disease
10 is selected from the group consisting of deep leg vein
thrombosis, reocclusion after a bypass operation or
angioplasty (PT(C)A), occlusion in peripheral arterial
disease, pulmonary embolism, disseminated intravascular
coagulation, coronary thrombosis, stroke, and the occlusion
15 of a shunt or stent.

15. A method for providing antithrombotic support in
thrombolytic treatment utilizing rt-PA or streptokinase,
20 which comprises administering a therapeutically effective
amount of a compound according claim 1, 2, 3, 4, 5, 6, 7,
8, 9, or 10, wherein E denotes an $R_bNH-C(=NH)-$ group, or a
physiologically acceptable salt thereof.

25 16. A method for preventing metastasis or the growth of
clot-dependent tumours, which comprises administering a
therapeutically effective amount of a compound according
claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes
30 an $R_bNH-C(=NH)-$ group, or a physiologically acceptable salt
thereof.

17. A method for treating or preventing fibrin-dependent inflammatory processes, which comprises administering a therapeutically effective amount of a compound according claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes an $R_pNH-C(=NH)-$ group, or a physiologically acceptable salt thereof.

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Attorney Docket No. 5/1213